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10/506,524	03/03/2005	Shishan Ji	1547/2	3049

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JENKINS, WILSON, TAYLOR & HUNT, P. A.
SUITE 1200, UNIVERSITY TOWER
3100 TOWER BOULEVARD
DURHAM, NC 27707

EXAMINER	
GUDIBANDE, SATYANARAYAN R	
ART UNIT	**PAPER NUMBER**
1654	
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08/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,524	JI ET AL.	
	Examiner	Art Unit	
	Satyanarayana R. Gudibande	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 20-22* is/are pending in the application.

4a) Of the above claim(s) *12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-18 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group XIV (claim 10) drawn to a conjugate for the formula shown in claim 1, wherein TA is alkaloids, and election of species, example 5 disclosed in the specification wherein the TA is camptothecin glycine ester which is an alkaloid in the reply filed on 5/31/07 is acknowledged. The election was made without traverse "with an understanding that under 'election of species' practice, it is understood that upon finding of an allowable species, examination will continue until all species have been examined, or a non-allowable species is found (page 9 of remarks filed on 5/31/07)".

Claim 10 drawn to the genus of alkaloids was examined in part to the extent it reads on the genus alkaloids. The genus of alkaloids comprises innumerable compounds whose structural characteristics have been either recited or disclosed in the instant application with the exception of the elected species camptothecin glycine ester. The elected species a conjugate of camptothecin glycine ester was searched and was found to be free of art. The search was extended to the generic formula of claim 1 and was found to be free of art. The search was further extended to the formula shown in claim 7 and was found to be free of art.

Claims 1-18 and 20-22 are pending.

Claim 12 have been withdrawn from further consideration as being drawn to non-elected species, because, cinobufagin is a steroid, clycyrrhetinic acid is an organic acid and scopoletin belongs to a class of coumarins.

Claims 1-11, 13-18 and 20-22 are examined on the merit to the extent that the claims read on the elected species camptothecin glycine ester, which is an alkaloid.

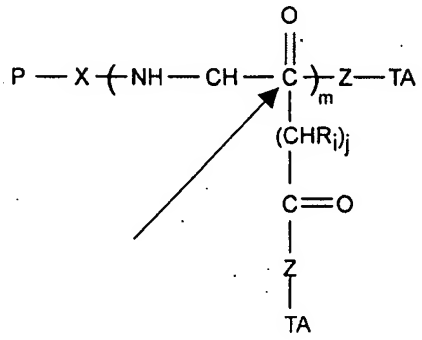
New matter rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 13, 14 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims have been amended to recite a formula in the amended claim 1 that has a carbon atom that exhibits a valency of 5 (the arrow pointing to the carbon with a valency of 5).



Lack of Ipsis Verbis Support

The specification lacks any Ipsis Verbis support that would support the chemical structure for the formula as presented in claim 1. The specification discussing support for the structure of claim 1 on page 2, does not provide support for the structure of the formula as depicted in claim 1.

Lack of Implicit Support

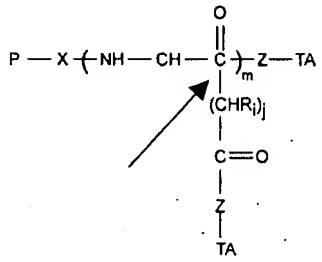
It is acknowledged that there is, it should be noted, that exact terms need not be used *in haec verba* to satisfy the written description requirement of the first paragraph of 35 U.S.C. 112. Newly added claims or amendment can be supported by implicit, or inherent disclosure. However, the specification also lacks any implicit or inherent disclosure that shows the structure of the formula as shown in claim 1 of the instant application. To the contrary, the specification teaches a formula where the valency of all the atoms are properly satisfied.

In conclusion, the specification does not provide reasonable support to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention as amended.

Written Description

Claims 1-11, 13-18 and 20-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the

claimed invention. In the instant application, applicants claim a conjugate of hydrophilic polymer-multicarboxyl oligopeptide and drug molecule of the following formula:



wherein,

P is a water soluble polymer; m is an integer from 2-12 inclusive;

j is an integer from 1-6 inclusive;

R_i is a group selected from the group consisting of H, C1-12 alkyl, substituted aryl, aralkyl, heteroalkyl and substituted alkyl;

X is a linking group;

Z is a linking group selected from O and NH; and

TA is a drug molecule.

The MPEP clearly states that the purpose of the written description is to ensure that the inventor had possession of invention as of the filing date of the application, of the subject matter later claimed by him. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir.1997). The MPEP lists factors that can be used to determine if sufficient evidence of possession has been

furnished in the disclosure of the application. These include, "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed invention is sufficient" MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated, "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. The MPEP further states that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although, the MPEP does not define what constitute a sufficient number of representatives, the courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant application, claims 1 and 7 recite a limitation, 'P' as a water-soluble polymer. The claim as recited encompass any and all polymer molecules that are water soluble which comprises of myriads of polymer molecules that includes all natural and synthetic polymers. The specification discloses, for e.g., polyethylene glycol, polypropylene, polyvinyl alcohol, polyacrylmorpholine or copolymer thereof, among them, polyethylene glycol and its copolymer are preferable and acidic oligopeptide of amino acid, especially oligopeptide of glutamic acid. The specification only has specific examples related to polyethylene glycol and oligopeptide of glutamic acid (a dimer of the peptide).

The claims 1 and 7 also recite a limitation, 'X' as a linking group wherein the X is not defined adequately neither in the claim as recited nor in the specification. Hence, 'X' as a linking group encompass any and all known and unknown compounds. The specific examples 1-5 (pages 9-13) discloses only $(CH_2)_2OCO$ as the linker. The specification is silent with respect to all the myriads of any and all linking groups as recited in the claims.

The claims 1 and 7 recite a limitation 'TA is a drug molecule' and claim 15 recites the term "PT is a drug molecule". The term "drug molecule" lacks proper definition as recited in the claims and as disclosed in the specification. The specification on page 8, lines 5-13 page 8, provides a broad definition for the drug molecule as "drug molecule including, for example, amino acids, proteins, enzymes, nucleosides, saccharides, organic acids, glycosides, flavonoids, quinones, terpenoids, phenylpropanoid phenols, steroids and glycosides thereof, alkaloids and the like the ingredient of nature medicine used in the treatment of tumor, such as paclitaxel, camptothecin, hydroxylcamptothecin, etoposide and the derivatives thereof". Therefore, the term "drug molecule" as defined includes all natural compounds. Since the definition comprises of

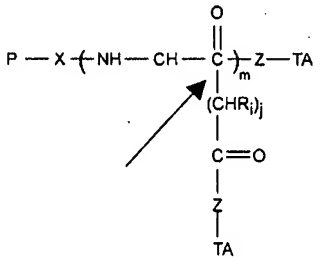
"derivatives thereof", it encompasses all the known and unknown derivatives all the natural compounds. However, the specific examples include only a handful compounds 'paclitaxel, camptothecin, cinobufagin, clycyrrhetinic acid, scopoletin'. Hence the number of specific compounds as in "drug molecules" disclosed does not commensurate with scope of the claims as recited.

Claims 17 and 21 recite a limitation, "another therapeutically active ingredient". The limitation lacks adequate written description in terms of a proper definition as recited in the claims. The specification on page 8, line 24 mentions that the composition may also include other medical agents. Therefore, the claim as recited and specification as disclosed is vastly inadequate in providing a proper definition associated with structural feature for the limitation "another therapeutically active ingredient".

Therefore, the claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Enablement Rejection: How to make?

Claims 1-11, 13 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In the instant application, applicants claim a conjugate of hydrophilic polymer-multicarboxyl oligopeptide and drug molecule of the following formula:



wherein,

P is a water soluble polymer; m is an integer from 2-12 inclusive;

j is an integer from 1-6 inclusive;

R_i is a group selected from the group consisting of H, C1-12 alkyl, substituted aryl, aralkyl, heteroalkyl and substituted alkyl;

X is a linking group;

Z is a linking group selected from O and NH; and

TA is a drug molecule.

The structure of the compound in the formula shown above depicts a carbon atom (indicated by an arrow) having a valency of 5. The specification as disclosed does not enable one of ordinary skill in the art, how to make the conjugate shown in the above formula.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (Wands, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the

invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the amount of direction or guidance presented; (6) the presence or absence of working examples; and (7) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to a conjugate of hydrophilic polymer-multicarboxyl oligopeptide as shown in the above formula. The nature of the invention encompasses a linker moiety, a hydrophilic polymer and a multicarboxyl oligopeptide. The conjugate of the instant invention comprises of a drug molecule that is attached to the polymer conjugate. However, the structure of the formula in claim 1 depicts a valency of 5 for one of the carbon atoms in the formula. The breadth of the claim is determined by the type of drug molecule conjugated to the polymer conjugate as recited in claim 10. The claims have been examined to the extent that they read on the elected species camptothecin, which belongs to the genus of alkaloids. The genus of alkaloids is very vast encompassing innumerable compounds. However, the specification is silent on other species of alkaloids that belongs to the genus. Thus, the claims as recited encompass a large number of compounds conjugated to the hydrophilic polymer-multicarboxyl oligopeptide.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The state of the prior art is a "scientific fact" as illustrated by Solomons, et al., Organic Chemistry, 2004, John Wiley & Sons., in Chapter 1 and on page 4 clearly teaches that the carbon atom is tetravalent and it can form 4 bonds. Even though, the cited reference is a text book published in the year 2004, the aforementioned scientific fact is well known in the art since 1860's.

The information available on the website: "http://web.archive.org/web/20000414203748/http://members.aol.com/logan20/outline1.html" also clearly reiterates that carbon is tetravalent and can form four covalent bonds (page 2, paragraph 2).

The above references clearly illustrate the fact that the carbon forms 4 bonds because it is tetravalent. However, the structure as shown in claim 1 of the instant application depicts a valency of five for the carbon atom as indicated by the arrow. The compound of the formula as shown in claim 1, is not supported in the specification as to how to make the compound. Therefore, the unpredictability of the art stems from the fact that the compound of the formula as shown in claim 1 is not supported adequately in the specification wherein the compound could be synthesized with a valency of 5 for the carbon atom.

(5) The amount of direction or guidance presented and (6) the presence or absence of working examples:

The specification is silent on how to make the compound of formula as depicted claim 1 of the instant application. The specification does not provide even one example of a compound wherein a compound with a carbon atom that exhibits a valency of 5 can be synthesized.

(7) The quantity of experimentation necessary:

Considering the state of the art as discussed by Solomons, et al., and the information available from the website, "http://web.archive.org/web/20000414203748/http://members.aol.com/logan20/outline1.html", one of ordinary skill in the art would be burdened with undue experimentation to practice the invention, because, it is not known in the art how to make the compound of formula shown in claim 1 with a valency of 5 for the carbon atom as indicated by the arrow. The specification does not provide any examples as to how to make the compound of formula as shown in claim 1 with a valency of 5 for the carbon atom.

It is the Examiner's position that one skilled in the art could not practice the invention as recited in the claims without undue experimentation. Therefore, the claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1-11, 13-18 and 20-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim 1, as recited has a carbon atom that exhibits a valency of 5 for the carbon atom in the formula as shown above. The claim is indefinite because, the carbon has a valency of 4 and can form four covalent bonds.

Claim 7 recites a limitation "P is a water soluble polymer". The variable "p" is not to be found in the formula as presented in claim 7. It is unclear as to what applicants are referring the "P" variable to in the formula.

Claims 14 and 15 recite "derivatives thereof" in defining the antitumor agent and drug molecule respectively. It is unclear from the claims as recited as to the nature of the derivatives of these antitumor agent and drug molecules. Neither the claims as recited nor the specification as disclosed define the "nature of these derivative of antitumor agent and drug molecules". It is unclear about the types of changes and modifications that could be made to the molecules to be claimed as derivatives.

Therefore, the claims as recited are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Information Disclosure Statement

No information disclosure statement (IDS) has been submitted with the application. The specification lists several patent references on page 2, nevertheless they have not been submitted on an IDS. The listing of references in the specification is not a proper information disclosure

statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Satyanarayana R. Gudibande, Ph.D.
Art Unit 1654

8/1/07
ANISH GUPTA
PRIMARY EXAMINER